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EXAMINER	
OGUNBIYI, OLUWATOSIN A	
ART UNIT	PAPER NUMBER
1645	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/575,836	BRUCK ET AL.	
	Examiner	Art Unit	
	OLUWATOSIN OGUNBIYI	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29 and 36-42* is/are pending in the application.

4a) Of the above claim(s) *1-12,21-23,28,29,36-40 and 42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-20,24-27 and 41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 April 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/13/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-29 and 36-42 are pending in the application. Claims 13-20,24-27 and 41 are under examination.

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Drawings

New corrected drawings are required in this application because the drawings (fig. 1A-B) contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. § 1.821-1.825 because the figures do not identify the sequences by a sequence identification number (SEQ ID NO)

Full compliance with the sequence rules is required in response to this office action. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Specification

The disclosure is objected to because of the following informalities: the specification on p. 34 line 33-34 contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. § 1.821-1.825 because the sequence is not identified by a sequence identification number (SEQ ID NO). Appropriate correction is requested.

Information Disclosure Statement

The information disclosure statement filed 4/13/06 has been considered. An initialed copy is enclosed.

Election/Restrictions

Applicant's election without traverse of Group III claims 13-28, 41 and 42 and species cancer, SEQ ID NO: 1, MAGE and 3D-MPL in response to the election/restriction requirement mailed 11/16/07 is acknowledged.

Claims 1-12, 21-23,28-29 and 36-40 and 42 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected non-invention or specie, there being no allowable generic or linking claim.

Claim Objections

Claim 14 does not further limit the combined preparation of claim 13. The combined preparation of claim 13 comprises: 1) IL-18 and 2) an immunogenic composition comprising an antigen and a CpG adjuvant and are *de facto* an admixture. The dictionary definition of combine – is to join or mix together (Compact Oxford Dictionary). The recitation of *admixed* in claim 14 does not further limit claim 13.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 13 and 20 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 17 of copending Application No. 10575836 ('836). Although the conflicting claims are not identical, they are not patentably distinct from each other because:

The instant claims are drawn to a combined preparation comprising as active ingredients the following individual components: (1) an IL-18 polypeptide or bioactive fragment or variant thereof and (2) immunogenic composition comprising an antigen and a CpG adjuvant, the active ingredients being for the simultaneous, separate or sequential use for the prophylaxis and/or treatment of infectious diseases, cancer, autoimmune diseases and related conditions, wherein the immunogenic composition additionally comprises 3D-MPL.

The '836 claim teach a combined preparation comprising as active ingredients the following individual components: (1) an IL-18 polypeptide or bioactive fragment or

variant thereof and (2) immunogenic composition comprising an antigen and a saponin adjuvant wherein said immunogenic composition additionally comprises 3D MPL and CpG oligonucleotide (claim 17 of '836 teaches a combination of two or more of said adjuvants listed in claim 17).

Thus, the '836 claim are obvious over the instant claims as the '836 claim teaches the instant composition i.e. (1) an IL-18 polypeptide or bioactive fragment or variant thereof and (2) immunogenic composition comprising an antigen and a CpG adjuvant, wherein the immunogenic composition additionally comprises 3D-MPL.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13-20 and 24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to combined preparation comprising as active ingredients the following individual components: (1) an IL-18 polypeptide or variant thereof (or derivative thereof) and (2) immunogenic composition comprising an antigen and a CpG adjuvant, the active ingredients being for the simultaneous, separate or sequential use for the prophylaxis and/or treatment of cancer.

The instant claims contemplate the use of a variant of Il-18 polypeptide. The instant specification teaches on p. 24 lines16-17 that variants may be used in which several, 5-10, 1-5, 1-3, 1-2 or 1 amino acids are substituted, deleted or added in any combination. Thus, the genus of IL-18 variants is very large and comprises species with different structure due to the plethora of several, 5-10, 1-5, 1-3, 1-2 or 1 amino acids substitutions or deletions and combination of substitutions and deletions of that can be made to the IL-18 polypeptide sequence. The instant specification does not correlate the common structure of the numerous number of variants that can be made with the function of IL-18. The specification is devoid of any description (e.g. by common structure) of a representative number of species present in the genus of said variants. The disclosure of the murine and human Il-18 sequences is not representative of the plethora of variants that can be made and which function similarly to IL-18. Jonak et al

(Journal of Immunotherapy 25 (Suppl. 1): S20-S27, 2002) discloses that murine and human interleukin 18 (IL-18) cDNA encode a precursor protein consisting of 192 and 193 amino acids, respectively which is then processed (by caspases) into a bioactive mature protein of 157 amino acids. The instant specification does not teach which several, 5-10, 1-5, 1-3, 1-2 or 1 amino acids and combinations of said amino acids can be deleted or substituted in the amino acid sequence of the IL-18 polypeptide and still retain function (p. 24). Furthermore, the instant claims contemplate the use of a derivative thereof of Il-18 polypeptide. The instant specification teaches that derivatives or variants include isolated polypeptides comprising an amino acid sequence which has at least 70% or 80% or 85% or 95% or 97-99% identity to SEQ ID NO: 6 or 7 (p.23). Seq ID NO: 6 and 7 are both 157 amino acids long and appear to be the mature bioactive IL-18. The instant specification does not teach the minimum sequence of SEQ ID NO: 6 or 7 necessary for its biological activity or function. The instant specification does not teach which amino acids e.g. which 30% or 20% or 15% or 5% or 3%-1% of SEQ ID NO: 6 or 7 can be changed and still maintain the function. Said derivatives or variants make up a large genus as any 30% or 20% or 15% or 5% or 3%-1% can be changed. The specification does not teach the common structure of said genus responsible for the function of the bioactive proteins. Absent sufficient description of the genus of said variants and derivatives one of skill in the art would not recognize that applicants had possession of said variants and derivatives contemplated in the instant invention.

Claim 13-20,24-27 and 41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a combined preparation comprising as active ingredients the following individual components 1) an IL-18 polypeptide or bioactive fragment and 2) immunogenic composition comprising MAGE family tumor associated antigen and a CpG adjuvant, the active ingredients being for the simultaneous use for the treatment of MAGE positive cancer, does not reasonably provide enablement for treatment of non-MAGE positive cancer.

The claims are also enabled for said combined preparation wherein said immunogenic composition comprising MAGE family tumor associated antigen and a CpG adjuvant is being for the separate use for the treatment of MAGE positive cancer.

The claims are not enabled for said combined preparation wherein said IL-18 polypeptide is for separate use for treatment of cancer. The claims are also not enabled for said combined preparation wherein said immunogenic composition comprising MAGE family tumor associated antigen and a CpG adjuvant is being for the separate use for the treatment of non-MAGE positive cancer. In addition, the claims are not enabled for prophylaxis of cancer using said combined preparation, the active ingredients for simultaneous, separate or sequential use. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to a combined preparation comprising as active ingredients the following individual components: (1) an IL-18 polypeptide or bioactive fragment or

variant thereof and (2) immunogenic composition comprising an antigen and a CpG adjuvant, the active ingredients being for the simultaneous, separate or sequential use for the prophylaxis and/or treatment of cancer.

The nature of the invention is a prophylactic or preventative treatment for cancer. The nature of the invention is also drawn to treatment of ongoing cancer.

Prophylaxis or prevention of Cancer

The scope of cancer is extremely broad and comprises cancers of many organ systems of the body (skin, lung, breast , colon, prostrate, neck , head, throat, blood, ovary cervix, testes etc). Cancer is a very complex process and there are currently no preventative treatments for cancer. Chamberlain (Expert Opinion on Pharmacotherapy, 1(4): 603-614, 2000) teaches that while vaccines are classically administered prophylactically to evoke an immune response capable of providing protection against infection by the same or similar pathogens for the treatment of infectious diseases, this has not been the approach in the field of cancer immunotherapy. Cancer is not an infectious process. Cancer cells express a limitless number of antigens and a priori knowledge of whom in the population is at risk for which cancer is lacking (see page 604, 1st column, first full paragraph). As such, 'anticancer vaccines' are called upon to evoke an immune response subsequent to antigen exposure rather than before it. If anticancer vaccines are to be utilized successfully, they must evoke an immune response capable of eradicating existing tumor. In the instant case, the specification has not established

guidance as to determine *apriori* the appropriate time prior to the development of cancer to begin any preventative/prophylaxis treatment for cancer.

The scope of the claims is also drawn to the use of any antigen including cancer or tumor antigens (e.g. MAGE) in said preparation for prophylaxis or prevention of cancer. The instant specification does not establish the role for tumor antigens and non-tumor associated antigens (e.g. a malaria antigen or fungal antigen or any non-tumor related self antigen) in the instant preparation for prophylaxis or prevention of cancer.

The scope of the claims also includes the simultaneous, separate or sequential use of the individual ingredients of the instant preparation i.e. 1) an Il-18 polypeptide or bioactive fragment or variant or derivative and 2) a composition comprising an antigen and CpG adjuvant. The art clearly teaches that prevention/prophylaxis of cancer is not a recognized approach for cancer therapy. Thus, the ingredients of the instant preparation are not enabled for prevention of cancer when they are used simultaneously or separate or sequentially and the instant application has not provided evidence to the contrary.

Therefore, one of ordinary skill in the art would not know how to use the instant preparation or its individual components for the simultaneous, separate or sequential use for the prophylaxis/prevention of cancer.

Treatment of Cancer

The scope of cancer is extremely broad and comprises cancers of many organ systems of the body (skin, lung, breast , colon, prostrate, neck , head, throat, blood, ovary cervix,

testes etc). Cancer is a very complex process and it treatment is also complex and depends on many factors. For active immunotherapy against ongoing cancer several factors affect the outcome of treatment of ongoing cancer. Such, factors include the choice of tumor antigen (different antigens are specific for different cancers, See Chamberlain, p. 605 table 1), intact antigen processing and presentation in the host and tumor, appropriate vector to deliver the antigen (whole tumor cells, peptide antigens etc. See Chamberlain p. 2000 table 2), use of adjuvants, route of administration and dosing regimen (See Chamberlain p. 604 left column bottom of first full paragraph).

Claims 13 and 25 are drawn to the treatment of any cancer using a preparation comprising any antigen with CpG adjuvant and Il-18. It is unpredictable whether a tumor antigen such as the viral protein HPV 16 E6/E7 associated with cervical cancer or a MAGE tumor associated antigen, each antigen with a CpG adjuvant can treat all other types of cancers. It is also unpredictable whether said antigens with CpG adjuvant and Il-18 can treat all other types of cancers. The art is devoid of any teaching of the use of one tumor antigen (with or without adjuvants Il-18 and CpG) as a universal treatment for all types of cancer and the instant specification does not correlate the use of any one tumor antigen to treat the full scope of the different cancers. Furthermore, it is noted that the scope of antigen comprises non-tumor associated antigens. For example, can a malaria antigen be used in the instantly claimed preparation to treat any type of cancer? For the MAGE antigen, the art does teach that preparation of a MAGE protein with adjuvants; a MAGE peptide; and a MAGE protein with CpG adjuvant have shown positive therapeutic benefits in human patients who have MAGE positive cancer/tumor

(Marchand et al European Journal of Cancer 39 (2003) 70-77, Marchand et al Int. J. Cancer: 80,219-230 (1999), Kruit et al Proc Am Soc Clin Oncol 21:2002 (abstract 1854). The instant specification does not correlate treatments with the instant preparation comprising MAGE with a positive therapeutic outcome for non-MAGE-positive cancers.

As to the separate use of Il-18 for the treatment of cancer, many studies have demonstrated the anti-tumor activity of Il-18 in murine tumor models (Jonak et al Journal of Immunotherapy 25 (Suppl. 1):S20-S27; Soos et al Clinical Immunology 109 (2003) 188-196, p. 188 last sentence of right column). The instant specification on p. 37 teaches that 20% of mice inoculated with tumor cells (mice tumor model expressing HER-2/neu) and then injected at day 7 to day 27 with murine Il-18 remain tumor free. However, the instant specification does not correlate Il-18 treatment with a positive therapeutic benefit for all types of cancers. The instant specification also does not correlate the results in the mouse model with a positive therapeutic benefit in humans using human Il-18. Although Il-18 has been shown to promote activation of Th1, B and dendritic cells, induce cytotoxic T cell generation and enhance natural killer cells cytolytic activity in mice and non-human primates (Herzyk et al. Toxicologic pathology, 31: 554-561, 2003) there is no correlation with treatment of cancer in humans. The art at the time of filling teaches that Il-18 is still a novel candidate therapy for cancer in humans (Jonak et al, 2002 p. S25 right column last sentence of first incomplete paragraph and Soos et al, 2003 p. 189 left column last sentence of first incomplete paragraph). It is art recognized that for any novel therapy, the transition from the laboratory to the clinic (Petri dish experiments to animal experiments to bedside) is a

quantum leap (Chatterjee et al. Cancer Immunol Immunother. 1994 38:75-82). Animal models are unpredictable for predicting efficacy in human cancer patients (Gura. Science vol. 278:1041-1042). Thus, for an unpredictable art such as cancer treatment, more guidance and working example is needed. One skilled in the art would therefore conclude that evidence obtained with murine Il-18 in one type of mice cancer model would not correlate with human Il-18 treatment of all types of cancer in human patients. Il-18 may provide adjuvant effects together with cancer specific immunotherapy since it promotes activation of Th1, B and dendritic cells, induce cytotoxic T cell generation and enhance natural killer cells cytolytic activity.

Thus, in view of the above considerations, while the claims are enabled for a combined preparation comprising as active ingredients the individual components 1) IL-18 and 2) an immunogenic composition comprising MAGE family tumor associated antigen and a CpG adjuvant the active ingredients being for the simultaneous treatment of non-metastatic MAGE positive cancers and enabled for said combined preparation wherein said immunogenic composition comprises MAGE family tumor associated antigen and a CpG adjuvant as a separate treatment for MAGE-positive cancer, one of skill in the art would not know how to use the instant invention to practice the full scope of the claims to treat all cancers.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13-20,24-27 and 41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Independent claims 13 and 25 are drawn to a combined preparation comprising as active ingredients the following individual components: (1) an IL-18 polypeptide or bioactive fragment or variant thereof and (2) immunogenic composition comprising an antigen and a CpG adjuvant, the active ingredients being for the simultaneous, separate or sequential use for the prophylaxis and/or treatment of cancer.

It is not clear in the independent claims 13 and 25, as written, how the preparation is a *combined* preparation but then the active ingredients in the combined preparation are for separate or sequential use because combined implies that the said ingredients of the preparation are mixed.

As to claims 25-27 and 41, how does a kit comprise active ingredients? How does the recitation of *active* modify the kit?

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 13-15, 19 and 24 are rejected under 35 U.S.C. 102(e) as being anticipated by Schwartz et al US 6,562,798 B1, May 13, 2003 filed June 1, 1999

Schwartz et al teaches a combined preparation comprising a modified immunostimulatory sequence (ISS) comprising a CpG sequence (column 7 lines 41-60 i.e. CpG adjuvant), and antigens (e.g. a tumor antigen and immunogenic derivatives (tumor cell extracts, tumor protein subunits, column 11 lines 13-40), and an adjuvant such as IL-18 (column 4 lines 59-61, column 11 lines 55-65, column 12 lines 15-24, column 12 lines 41-50). Schwartz teaches that said immunostimulatory sequence (CpG adjuvant) comprises a purine, C, G, pyrimidine, pyrimidine sequence and teaches said combined preparation as a solution for injection (column 23 lines 23-30).

Claim Rejections - 35 USC 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 13-19 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kruit et al Proc am soc Clin Oncol 21:2002 (abstract 1854) in view of Schwartz et al US 6,562,798 B1, May 13, 2003 filed June 1, 1999 and Johnson et al WO 995965 A1, Nov. 1999.

The claims are drawn to a combined preparation comprising as active ingredients the following individual components: (1) an IL-18 polypeptide and (2) immunogenic composition comprising antigen and a CpG adjuvant.

Kruit et al teaches a preparation comprising a composition comprising a MAGE family (MAGE 3) tumor associated antigen and a CpG adjuvant admixed together in the

form of an injectable solution (since patients were vaccinated intramasucularly). Kruit teaches said preparation for the treatment of metastatic MAGE-3 positive melanoma.

Kruit et al does not teach Il-18 (interleukin 18) polypeptide or bioactive fragments thereof such as human or murine Il-18 (i.e. SEQ ID NO: 6 or SEQ ID NO: 8) in said preparation and does not teach said CpG adjuvant comprising purine, C, G, pyrimidine, pyrimidine sequence

Schwartz et al teaches a combined preparation comprising a modified immunostimulatory sequence (ISS) comprising a CpG sequence (column 7 lines 41-60 i.e. CpG adjuvant), and a tumor antigen and immunogenic derivatives (tumor cell extracts, tumor protein subunits) (column 11 lines 13-40), and an adjuvant such as Il-18 (column 4 lines 59-61, column 11 lines 55-65, column 12 lines 15-24, column 12 lines 41-50). Schwartz teaches said immunostimulatory sequence comprises a purine, C, G, pyrimidine, pyrimidine sequence (CpG adjuvant) and teaches said combined preparation for injection (column 23 lines 52-53). Schwartz et al teaches that said immunostimulatory sequence (CpG sequence) provides adjuvant like activity in the generation of a Th1-type immune response to a tumor antigen (column 6 lines 9-14 and line 66 to column 7 lines 1-6). Schwartz teaches that Il-18 acts as an immunomodulatory facilitator which supports and/or enhances the immunomodulatory activity of said modified immunostimulatory sequence (column 11 lines 54-67 to column 12 lines 1-24).

Johnson et al teaches human and murine IL-18 polypeptide of SEQ ID NO: 6 and 7 respectively which are the bioactive fragments of IL-18 polypeptide (see SEQ ID NO: 1 and 2 of Johnson et al and attached sequence alignment).

It would have been prima facie obvious to one of ordinary skill in the art at the time the instant invention was made to include Il-18 polypeptide or its bioactive fragment (i.e. human or murine IL-18) in the preparation of Kruit et al, as taught by Schwartz et al and Johnson et al because Schwartz et al teaches that IL-18 can be used as an adjuvant in a preparation comprising an immunostimulatory sequence comprising CpG and a tumor antigen, to support and/or enhance the immunomodulatory activity of said immunostimulatory sequence and Johnson et al teach the bioactive IL-18 i.e. human Il-18 or murine Il-18 (the instant SEQ ID NO: 6 and SEQ ID NO: 7) which can be added to the composition of Kruit et al with a reasonable expectation of success.

It would also have been prima facie obvious to one of ordinary skill in the art at the time the instant invention was made to, in addition, substitute the CpG adjuvant of Kruit et al with the CpG adjuvant (comprising a Purine, C,G, pyrimidine, pyrimidine sequence) of Schwartz et al because Schwartz et al teach that said CpG adjuvant comprising a Purine, C,G, pyrimidine, pyrimidine sequence provides adjuvant like activity in the generation of a Th1-type immune response to a tumor antigen.

Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kruit et al Proc am soc Clin Oncol 21:2002 (abstract 1854) and Schwartz et al US 6,562,798 B1, May 13, 2003 filed June 1, 1999 and Johnson et al WO 995965 A1, Nov. 1999 as applied to claims 13-19 and 24 above further in view of Marchand et al. Int. J. Cancer: 80, 219-230 (1999).

The combination of Kruit and Schwartz and Johnson is set forth supra. Said combination does not teach an immunogenic derivative of the tumor associated antigen MAGE.

Marchand et al teach a composition comprising an antigenic peptide (immunogenic derivative) of the tumor associated antigen MAGE (p. 220 left column under vaccination) used for the treatment of melanoma/MAGE positive tumors.

It would have been prima facie obvious to one of ordinary skill in the art at the time the instant invention was made to substitute the MAGE full length protein of the combined preparation of Kruit et al and Schwartz and Johnson et al as combined with the MAGE antigenic peptide of Marchand et al because Marchand et al teach that a MAGE antigenic peptide can also be used to treat MAGE positive tumors.

Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kruit et al Proc am soc Clin Oncol 21:2002 (abstract 1854) and Schwartz et al US 6,562,798 B1, May 13, 2003 filed June 1, 1999 and Johnson et al WO 995965 A1, Nov. 1999 as

applied to claims 13-19 and 24 above further in view of Chen et al. Expert Opnin. Ther. Patents (2001) 11(6):937-950.

The combination of Kruit and Schwartz and Johnson is set forth supra. The combined preparation of Kruit and Schwartz and Johnson as combined does not additionally comprise the immunostimulant chemical 3D-MPL.

Chen et al teaches 3D-MPL as an adjuvant used to induce a Th1 immune response and used to potentiate immune recognition of a tumor associated antigen (p. 943 under Novel vaccine adjuvants and p. 944 table 5).

It would have been prima facie obvious to one of ordinary skill in the art at the time the instant invention was made to add the 3D MPL of Chen et al to the composition of Kruit et al and Schwartz and Johnson et al as combined supra because Chen et al teach 3D-MPL as an adjuvant used to induce a Th1 immune response and potentiate immune recognition of a tumor associated antigen.

Claims 25, 26, 27 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kruit et al Proc am soc Clin Oncol 21:2002 (abstract 1854) and Schwartz et al US 6,562,798 B1, May 13, 2003 filed June 1, 1999 and Johnson et al WO 995965 A1, Nov. 1999 as applied to claims 13-19 and 24 above further in view of Ray et al WO 99/11275 March 1999.

The claims are drawn to pharmaceutical kit comprising as the active ingredients the following individual components: (1) an IL-18 polypeptide and (2) immunogenic composition comprising antigen and a CpG adjuvant.

The combination of Kruit and Schwartz and Johnson et al is set forth supra. Said combination does not teach a pharmaceutical kit comprising said preparation of Kruit et al and Schwartz and Johnson et al.

Ray et al teach a kit comprising a CpG adjuvant (ISS-ODN) and any other additional medicaments e.g. an antigen (p. 4 lines 14-25).

It would be prima facie obvious to one of ordinary skill in the art to package the preparation comprising IL-18 polypeptide and composition comprising MAGE antigen and CpG adjuvant of Kruit and Schwartz and Johnson as combined in a kit format as taught by Ray et al because kits provide convenience and ease of use to the customer/patient to be treated with the ingredients of said preparation of Kruit and Schwartz and Johnson as combined.

Claims 25, 26, 27 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kruit et al Proc am soc Clin Oncol 21:2002 (abstract 1854) and Schwartz et al US 6,562,798 B1, May 13, 2003 filed June 1, 1999 and Johnson et al WO 995965 A1, Nov. 25, 1999 and Marchand et al. Int. J. Cancer: 80, 219-230 (1999) as applied to claim 16 above further in view of Ray et al WO 99/11275 March 1999.

The claims are drawn to pharmaceutical kit comprising as the active ingredients the following individual components: (1) an IL-18 polypeptide and (2) immunogenic composition comprising the immunogenic derivative of an antigen and a CpG adjuvant.

The combination of Kruit and Schwartz and Johnson and Marchand is set forth supra. Said combination does not teach a pharmaceutical kit comprising said preparation of Kruit et al and Schwartz and Johnson et al and Marchand et al.

Ray et al teach a kit comprising a CpG adjuvant (ISS-ODN) and any other additional medicaments e.g. an antigen (p. 4 lines 14-25).

It would be prima facie obvious to one of ordinary skill in the art at the time the instant invention was made to package the preparation comprising IL-18 polypeptide and composition comprising MAGE antigen and CpG adjuvant of Kruit and Schwartz and Johnson and Marchand as combined in a kit format as taught by Ray et al because kits provide convenience and ease of use to the customer/patient to be treated with the ingredients of said preparation of Kruit and Schwartz and Johnson and Marchand as combined.

Prior Art Pertinent to Applicants' Disclosure

1. Chaux et al. US 6,291,430 B1- discloses MAGE family peptides presented by HLA class II molecules.
2. Miconnet et al Journal of Immunology, 2002, 168:1212-1218 - teaches a CpG oligodeoxyribonucleotide (ODN 1826) comprising a Purine, C,G, pyrimidine,

pyrimidine sequence used as an adjuvant in cancer immunotherapy and stimulates a CTL response (see abstract, p. 1213 left column under synthetic peptides and CpG ODN and p. 1218 left column).

Status of the Claims

Claims 13-20, 24-27 and 41 are rejected. No claims allowed.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Oluwatosin Ogunbiyi whose telephone number is 571-272-9939. The examiner can normally be reached on M-F 8:30 am - 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisory Examiner Shanon Foley can be reached on 571-272-0898.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Oluwatosin Ogunbiyi/

Examiner, Art Unit 1645

/Patricia A. Duffy/

Primary Examiner, Art Unit 1645